REMARKS

Amendments to the Claims

Claim 31 has been amended to delete SEQ ID Nos. that are not CD8+ T cell epitopes of malaria.

Nonstatutory Obviousness-type Double Patenting

As noted in Applicants' Amendment filed on December 26, 2006, once the present claims of the subject application are deemed allowable, Applicants will submit a terminal disclaimer if the allowable claims cover subject matter that is not patentably distinct from the subject matter covered by the claims of U.S. Patent No. 6,663,871 and/or if the allowable claims cover subject matter that is not patentably distinct from the subject matter covered by the claims of U.S. Patent Application Nos. 10/833,439, 10/833,744, 10/833,745 and/or 10/653,624.

Applicants thank the Examiner for acknowledging that the double patenting rejection of Claims 1-6, 10, 14-16, 27 and 31-33 as being unpatentable over claims 1, 2, 5-7, 15-18, and 20 of U.S. Patent No. 6,663,871 "will be withdrawn upon Applicants' submission of a compliant terminal disclaimer" (Office Action, page 2). Applicants also thank the Examiner for acknowledging that the provisional nonstatutory double patenting rejections of Claims 1-3, 6, 7, 10, 12, 14 and 15 as being unpatentable over claims 1, 4, 5, 9, 11, 13, and 14 of copending Application No. 10/833,439 and over claims 1, 4, 5, 9, 11, and 13-16 of copending Application No. 10/833,744; Claims 1-3, 5-7, 10, 12, 14 and 15 as being unpatentable over claims 1, 4, 5, 9, 11, and 13-15 of copending Application No. 10/833,745; and Claims 1, 6 and 27 as being unpatentable over claims 1-5 and 6-8 of copending Application No. 10/653,624 "are held in abeyance until allowable subject matter is determined" (Office Action, pages 2-3).

Rejection of Claims 1-3, 6, 10, 12, 14 and 15 under 35 U.S.C. §103(a)

Claims 1-3, 6, 10, 12, 14 and 15 are rejected under 35 U.S.C. §103(a) "as being obvious over Pialoux *et al.* (1995) in view of Egan *et al.* (1995)" (Office Action, page 4). According to the Examiner, "it would be obvious to one skilled in the art to prime and boost a subject using a protein subunit and an ALVAC vector expressing the same epitope in either order with

reasonable expectation of success, absent evidence to the contrary" (Office Action, page 5). The Examiner further states that "Egan's disclosure that ALVAC-HIV elicits CTL response does not limit the disclosure to a specific order of priming and boosting regimen" (Office Action, page 5).

Applicants respectfully disagree. At the time of the invention, one of skill in the art would have understood that reversing the order of administration of the priming and boosting compositions in a heterologous prime-boost immunization regimen would not necessarily produce a CD8+ T cell response that is equivalent to the CD8+ T cell response generated using the reverse order of administration. In fact, one of skill in the art would have appreciated that reversing the order of administration of the priming and boosting compositions could result in a significantly lower CD8+ T cell response or no CD8+ T cell response at all. For example, Li *et al.* (Reference AU4 of record) reported that immunization with recombinant influenza virus followed by a recombinant vaccinia virus three weeks later "resulted in a 96.3% decrease of plasmodial rRNA in the liver, revealing a remarkable synergistic effect of the vaccination with two distinct live vectors," but that "***protective immunity failed to be induced*** when the two recombinant viruses were administered ***in the reverse order***" (Li *et al.*, page 5216, right column; emphasis added). A similar result is described by Applicants in the instant specification, which discloses that, upon immunization with recombinant MVA followed by recombinant DNA, a "low level of T cells was observed" but that a "very much higher level of CD8+ T cells was observed by boosting the DNA-primed immune response with recombinant MVA" (specification, page 31, lines 21-25; also see Figure 3).

Pialoux *et al.* "evaluated the safety and the immunogenicity of a new combined vaccine regimen consisting of priming with a recombinant canarypox virus expressing gp160 (MN) [vCP125] followed by boosters with a soluble recombinant envelope glycoprotein gp160 (MN/LAI) [rgp160] in HIV-seronegative volunteers at low risk of HIV infection" (Pialoux *et al.*, page 374, left column; emphasis added). Pialoux *et al.* clearly teach that their heterologous prime-boost method "was designed to evaluate . . . the capacity of this prime-boost association to induce both humoral and cellular responses" (Pialoux *et al.*, paragraph bridging pages 374 and 375).

Upon considering the teachings of Pialoux *et al.* as a whole, one of skill in the art would appreciate that Pialoux *et al.* administered the ALVAC vector expressing an HIV gp160 protein

prior to the recombinant gp160 protein in their heterologous prime-boost protocol because administering these agents in the reverse order would be unlikely to induce an efficient CD8+ T cell response, which was one of the two main objectives of their protocol. This becomes clear in light of the teaching in Pialoux *et al.* that "[r]ecombinant proteins can usually prime $CD4^+$ cells to induce antibody responses, but they are ***generally ineffective at inducing $CD8^+$ CTLs*** because of a failure to associate intracellularly with class I MHC antigens," while "[i]n contrast, recombinant vaccinia viruses infect target cells, resulting in intracellular expression of viral genes, and ***effectively induce class-I restricted $CD8^+$ CTL responses*** to the protein corresponding to the inserted gene" (Pialoux *et al.*, pages 379-380; emphasis added).

Thus, Pialoux *et al.* teach away from using a recombinant protein to induce a CD8+ T cell response and, therefore, provide no motivation to modify their heterologous prime-boost immunization protocol to include priming with a recombinant gp160 protein. Furthermore, by teaching that a recombinant protein is an ineffective agent for inducing a CD8+ T cell response, Pialoux *et al.* do not provide a reasonable expectation that priming with a recombinant HIV gp160 protein and boosting with an ALVAC vector expressing an HIV gp160 protein would successfully generate a CD8+ T cell response in a mammal.

The Egan *et al.* reference, which includes two authors of the Pialoux *et al.* reference (i.e., Enzo Paoletti and James Tartaglia), contains no teaching that contradicts the teaching in Pialoux *et al.* that recombinant protein is an ineffective agent for inducing a CD8+ T cell response. Egan *et al.* tested "whether immunization with ALVAC alone or in combination with subunit boosting could induce CTL in vaccinia-immune and -naive volunteers" (Egan *et al.*, abstract; emphasis added). Consistent with the teachings in Pialoux *et al.*, Egan *et al.* teach that "$CD8^+$ cytolytic T lymphocytes (CTL) . . . can be induced most effectively with live virus vectors" (Egan *et al.*, abstract). Egan *et al.* further teach that "[a]ttempts to induce HIV-1-specific $CD8^+$ CTL in humans by vaccination have had limited success. Purified recombinant HIV-1 env protein vaccines elicit $CD4^+$ CTL responses in a subset of persons who are immunized" (Egan *et al.*, page 1623, left column), thereby implying that previous attempts to induce HIV-1-specific CD8+ CTL in humans by vaccination with HIV-1 env recombinant protein have had limited success. Thus, the teachings in Egan *et al.* are consistent with those in Pialoux *et al.* regarding the

inefficacy of using a recombinant protein to induce CD8+ T cell responses against HIV in humans.

The combination of Pialoux *et al.* and Egan *et al.* teach a heterologous prime-boost method that includes priming with vCP125, an ALVAC expressing an HIV glycoprotein, and boosting with a recombinant HIV env protein (i.e., HIV gp160 or HIV gp120). The combination of Pialoux *et al.* and Egan *et al.* clearly do not teach or suggest that their heterologous prime-boost methods should be modified to include a prime with an HIV env protein and a boost with an ALVAC vector expressing the HIV env protein, nor does the combination provide any motivation to use a recombinant protein as a priming agent in a heterologous prime-boost method. Accordingly, it would not be obvious to one of skill in the art to reverse the order of the priming and boosting compositions in the methods of Pialoux *et al.* and Egan *et al.*

The combined teachings of Pialoux *et al.* and Egan *et al.* as a whole do not render Applicants' claimed invention obvious.

Rejection of Claims 1-3, 5, 6, 10, 12, 14 and 15 under 35 U.S.C. §103(a)

Claims 1-3, 5, 6, 10, 12, 14 and 15 are rejected under 35 U.S.C. §103(a) "as being obvious over Pialoux *et al.* (1995) in view of Egan *et al.* (1995), and further in view of Walker *et al.* (1989)" (Office Action, page 6). According to the Examiner, Applicants' arguments in the Amendment filed on December 26, 2006 "are not persuasive because the limitations not disclosed in Walker *et al.* have already been described in Pialoux *et al.* and Egan *et al.* as set forth above" (Office Action, page 6). The Examiner further states that the "instant rejection is based on the invention as a whole rather than Walker *et al.* alone" (Office Action, page 6).

As discussed above, the combination of Pialoux *et al.* and Egan *et al.* teach a heterologous prime-boost method that includes priming with vCP125, an ALVAC expressing an HIV glycoprotein, and boosting with a recombinant HIV env protein (i.e., HIV gp160 or HIV gp120). The combined teachings of Pialoux *et al.* and Egan *et al.* do not teach or suggest that their vaccination methods should be modified to include priming with a recombinant HIV env protein and boosting with an ALVAC vector expressing an HIV env protein because Pialoux *et al.* teach away from using a recombinant HIV env protein to induce a CD8+ T cell response in a human.

Walker *et al.* disclose "seven HIV-1 reverse transcriptase-specific cytotoxic T-lymphocyte (CTL) clones from the peripheral blood of two seropositive subjects" (Walker *et al.*, abstract) and teach that three of these seven lines were able to lyse cells incubated with peptide 50, which consists of the amino acid sequence NPDIVIYQYMDDLYVGSDLEIGQHR, in a CTL lysis assay in vitro (Walker *et al.*, page 9517, Table 4). Walker *et al.* do not teach or suggest that peptide 50 should be featured in a prime-boost method for generating a CD8+ T cell immune response in a mammal against a target antigen (e.g., HIV), nor do Walker *et al.* disclose or suggest administering to a mammal a boosting composition comprising a non-replicating or replication-impaired recombinant virus vector that is a source of any of the disclosed CD8+ T cell epitopes. Clearly, Walker *et al.* do not provide the teaching that is lacking in the Pialoux *et al.* and Egan *et al.* references that would render Applicants' claimed invention obvious.

The combination of Pialoux *et al.*, Egan *et al.* and Walker *et al.* do not render Applicant's claimed methods obvious because, as discussed above, Pialoux *et al.* teach away from using a recombinant HIV env protein to induce a CD8+ T cell immune response in a human and, therefore, provide no motivation to reverse the order of administering the priming and boosting vectors in their heterologous prime-boost method. Even if one of skill in the art were to make the improper combination, the combined teachings of Pialoux *et al.*, Egan *et al.*, and Walker *et al.*, at most, would have directed one of skill in the art to carry out a heterologous prime-boost method in a human that includes ***boosting with recombinant peptide 50***. This clearly differs from Applicants' claimed methods, which comprise boosting with a non-replicating or replication-impaired recombinant virus vector.

Thus, the combined teachings of Pialoux *et al.*, Egan *et al.* and Walker *et al.* do not render Applicants' claimed invention obvious.

Rejection of Claims 1-4, 6, 7, 10, 12, 14-16, 27, 28, 32 and 33 under 35 U.S.C. §103(a)

Claims 1-4, 6, 7, 10, 12, 14-16, 27, 28, 32 and 33 are rejected under 35 U.S.C. §103(a) "as being unpatentable over Li *et al.* (1993, reference No. AU4 in IDS filed on 06 July 2004) in view of Sutter *et al.* (1992, reference No. C52 in IDS filed on 09 November 2006) and Stoute *et al.* (1997, January)" (Office Action, page 7).

The Examiner cites Li *et al.* as describing "priming with recombinant influenza virus followed by boosting with recombinant vaccinia virus induces CD8+ T-cell-mediated protective immunity against malaria" and acknowledges that "Li *et al.* do not describe a replication-impaired or non-replicating recombinant virus vector in the boosting composition" (Office Action, page 7). The Examiner cites Sutter *et al.* as describing "a non-replicating vaccinia vector, modified vaccinia Ankara (MVA) strain that has been safety tested in humans" (Office Action, page 7). The Examiner cites Stoute *et al.* as describing "malaria vaccine formulations in three kinds of adjuvants" and "that SBAS2 is the most efficacious adjuvant" (Office Action, page 8).

According to the Examiner, "[i]t would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the priming and boosting compositions of Li *et al.* so as to replace the vaccinia vector with a safer non-replicating MVA vector as taught by Sutter *et al.* One having ordinary skill in the art would have been motivated to do this because a live vaccinia virus is infectious while MVA does not replicate in mammalian cells yet expresses recombinant genes efficiently, as suggested by Sutter *et al.*" (Office Action, page 8). The Examiner further states that "[i]t would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the priming and boosting compositions of Li *et al.* so as to further comprise the SBAS2 adjuvant as taught by Stoute *et al.*" (Office Action, page 8).

Applicants respectfully disagree. The combined teachings of Li *et al.* and Sutter *et al.* would not have motivated one of skill in the art to replace the replicating vaccinia virus in the boosting composition of Li *et al.* with the MVA vector of Sutter *et al.* because Li *et al.* teach away from modifying their heterologous prime-boost immunization regimen that includes priming with a recombinant influenza virus and boosting with a replicating vaccinia virus.

Specifically, Li *et al.* immunized mice with a recombinant influenza virus expressing an epitope from the circumsporozoite protein of *P. yoelii* known to be recognized by CD8+ T cells [influenza ME virus] followed by a recombinant vaccinia virus expressing the entire circumsporozoite protein (PYCS) and induced CD8+ T cell-mediated protective immunity against malaria. Li *et al.* teach that immunization with recombinant influenza virus followed by a recombinant vaccinia virus three weeks later "resulted in a 96.3% decrease of plasmodial rRNA in the liver, ***revealing a remarkable synergistic effect*** of the vaccination with two distinct

live vectors" but that "protective immunity ***failed to be induced*** when the two recombinant viruses were administered ***in the reverse order***" (Li *et al.*, page 5216, right column; emphasis added). Li *et al.* further emphasize that:

> Protective immunity can ***only*** be induced by a primer injection with influenza ME virus, followed by a booster injection with vaccinia PYCS virus, but not when the reverse protocol is followed

(Li *et al.*, page 5217, right column; emphasis added). Thus, Li *et al.* teach the critical importance of using a recombinant influenza virus prime and replicating recombinant vaccinia virus boost in their immunization method in order to achieve "a remarkable synergistic effect," and thus, clearly teach away from modifying their successful immunization method. Accordingly, Li *et al.* provide no motivation for one of skill in the art to substitute any other vector for either the recombinant influenza virus priming vector or recombinant vaccinia virus boosting vector in their protocol.

Sutter *et al.* also do not provide sufficient motivation for one of skill in the art to substitute their MVA vector for either the recombinant influenza virus priming vector or recombinant vaccinia virus boosting vector in the immunization method of Li *et al.* Sutter *et al.* examined "the potential of the modified vaccinia Ankara (MVA) strain as an expression vector because of its extreme attenuation" (Sutter *et al.*, page 10847, left column) and describe experiments in which human cells were infected *in vitro* with a single vaccinia virus vector, either an MVA strain or a Western Reserve strain that multiplies well in human cells. Sutter *et al.* found that "the expression of late, as well as early, viral genes was unimpaired in human cells despite the inability of MVA to produce infectious progeny" and that "recombinant viruses were able to synthesize high levels of a foreign protein in human cells" (Sutter *et al.*, page 10847, right column).

Notably, Sutter *et al.* do not teach that their MVA vector can elicit a CD8+ T cell response in a mammal. Moreover, Sutter *et al.* point to the uncertainty of using MVA in immunization methods in mammals by teaching that "[w]hether MVA vectors will also be useful for live vaccine or therapeutic applications remains to be determined" (Sutter *et al.*, page 10851).

The combined teachings of Li *et al.* and Sutter *et al.* do not suggest substituting the replicating vaccinia virus vector in the boosting composition of Li *et al.* with the MVA vector of Sutter *et al.* because Li *et al.* teach the "remarkable synergistic effect" and the critical importance

of using a recombinant influenza virus prime and replicating recombinant vaccinia virus boost in their immunization method and, thus, teach away from substituting the recombinant vaccinia virus boosting vector in their protocol with the MVA vector of Sutter *et al.*, while Sutter *et al.* teach the uncertainty of using their MVA vector for live vaccine or therapeutic applications.

The teachings in Sutter *et al.* that expression of viral genes was unimpaired and that expression of a foreign protein was high in human cells infected with MVA do not provide sufficient motivation to use the MVA vector in the protocol of Li *et al.* because Li *et al.* show that their two replicating viral vectors that express antigen at high levels are only able to elicit an immune response if administered in a particular order, and are unable to elicit an immune response when administered in the reverse order. Thus, the teachings of the combined references do not provide a reasonable expectation that an MVA vector would successfully generate a CD8+ T cell immune response against at least one target antigen in a mammal if used as a boosting vector in the method of Li *et al.*

In addition, at the time of Applicants' invention, those of skill in the art were of the opinion that "[t]o elicit an adequate immune response, ***live vaccine virus must replicate*** within the recipient" (Watson, J.C. and Peter, G., "General Immune Practices" in *Vaccines*, Plotkin, S.A. and Orenstein, eds., WB Saunders publ. 1999, Reference AT8 of record, page 57, right column; emphasis added). In further support of this, Applicants direct the Examiner's attention to the concurrently filed Exhibit, which is a Declaration of Dr. Mackett under 37 C.F.R. § 1.132 that was originally filed in support of the claimed invention in the parent application, U.S. Appl. No.09/454,204 (now U.S. Patent No. 6,663,871) to which priority is claimed under 35 U.S.C. § 120. In paragraphs 4 and 5 of the Declaration, Dr. Mackett states that:

> Prior to the teaching that a non-replicating or replication impaired virus is effective in boosting a CD8+ T cell response against an antigen in U.S. Application No. 09/454,204, it was generally accepted that replication competent viral vectors were required to provide effective and long lasting immunity. This belief was based on the expectation that a replication competent virus would produce more antigen in the host compared to a non-replicating or replication impaired virus

and that:

> Accordingly, prior to the teachings in U.S. Application No. 09/454,204, it was clearly not expected that a non-replicating or replication impaired virus would be

> as effective as a replicating virus in boosting a CD8+ T cell response against an antigen in a host.

These teachings, which were accepted by those of skill in the art at the time of the invention, provide an additional reason why one of skill in the art would not be motivated to substitute the replicating vaccinia virus vector in the boosting composition of Li *et al.* with the MVA vector of Sutter *et al.*

Stoute *et al.* do not provide the teaching that is lacking in the Li *et al.* and Sutter *et al.* references that would render Applicants' claimed invention obvious. Stoute *et al.* immunized human subjects with "a hybrid in which the circumsporozoite protein fused to hepatitis B surface antigen (HbsAg) was expressed together with unfused HbsAg" (Stoute *et al.*, page 86, column 2). Stoute *et al.* found that the vaccine "protects adults who have never been exposed to malaria against experimental challenge with *P. falciparum*", and that "[s]trong adjuvants were required" (Stoute *et al.*, page 90, column 1).

For the reasons discussed above, the combination of Li *et al.*, Sutter *et al.* and Stoute *et al.* clearly do not teach or suggest Applicant's claimed methods of generating a CD8+ T cell immune response in a mammal against at least one target antigen. Even if one of skill in the art were to make the improper combination, the combined teachings of Li *et al.*, Sutter *et al.* and Stoute *et al.*, at most, would have directed one of skill in the art to carry out the heterologous prime-boost method of Li *et al.* using a recombinant influenza virus priming composition and replicating recombinant vaccinia virus boosting composition, as taught by Li *et al.*, wherein the priming and boosting compositions comprise the SBAS2 adjuvant of Stoute *et al.*

Thus, the combined teachings of Li *et al.*, Sutter *et al.*, and Stoute *et al.* clearly do not render Applicants' claimed invention obvious.

Claim Objections

Claim 31 is objected to "as being of improper dependent form for failing to further limit the subject matter of a previous claim" (Office Action, page 9). The Examiner states that "Claim 31 recites a group of CD8+ T cell epitopes against other pathogens than malaria and hence fails to further limit base claim 27" (Office Action, page 9).

Applicants have amended Claim 31 to delete all references to SEQ ID Nos. that do not correspond to CD8+ T cell epitopes of malaria, thereby obviating the objection.

Fourth Supplemental Information Disclosure Statement

A Fourth Supplemental Information Disclosure Statement (SIDS) is being filed concurrently herewith. Entry of the SIDS is respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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